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14. ABSTRACT

Purpose: The purpose was to determine the optimal combination of lipid rescue and traditional ACLS therapy for treatment overdose of bupivacaine, desipramine, venlafaxine and bupropion. **Design**: This study was a prospective, experimental, mixed research design
Methods: For each drug studied, seven swine were assigned to eight ACLS or BLS protocol resuscitation groups: Vasopressin/Lipid; Epinephrine/Lipid; Lipid; Epinephrine; Vasopressin; Epinephrine/Vasopressin; Epinephrine/Lipid/Vasopressin; and CPR. Each subject was administered a toxic dose of the drug until there was a non-perfusing arrhythmia. Each resuscitation protocol was implemented. Survival was defined as return of spontaneous circulation to a systolic blood pressure ≥ 60 mm/Hg. **Sample**: The sample consisted of seven swine assigned to eight ACLS or BLS protocol resuscitation groups: Vasopressin/Lipid; Epinephrine/Lipid; Lipid; Epinephrine; Vasopressin; Epinephrine/Vasopressin; Epinephrine/Lipid/Vasopressin; and CPR. **Analysis**: An odds/ratio was used to analyze the data. **Findings:** As expected, the results varied according to the studied drug overdose. For example, with bupivacaine, seventy-one percent of the epinephrine/lipid group survived compared to 19% of all the groups without lipid therapy. The odds of survival for the epinephrine with lipids group was 8.5 fold greater than all the groups without lipid therapy. Epinephrine with lipid group had a five times greater odds for survival compared to epinephrine with vasopressin. Epinephrine alone offered a 4.5 times greater chance of survival when compared to the group that received lipid alone. No swine in the CPR or vasopressin group survived. With the desipramine study, 100% of the vasopressin group survived, whereas none of the epinephrine group survived ($p>.05$).
Implications for Military Nursing: This research grant offers possible treatment options for those individuals that have received a lethal toxic dose of the four selected drugs. It is imperative to be able to resuscitate patients from these potential lethal toxicities.

15. SUBJECT TERMS
ACLS therapy, ACLS or BLS protocol resuscitation, resuscitation

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PI Signature ______________________ Date 13 January 2015

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Abstract

Purpose: A toxic dose of bupivacaine and antidepressant drugs causes cardiac arrhythmias and ultimately asystole. Resuscitation is difficult and usually unsuccessful. Until recently, cardiopulmonary bypass was the only effectively treatment. Anecdotal evidence suggests that infusion of lipid emulsion may be an effective treatment. No studies have determined the optimal combination of lipid rescue and traditional Advanced Cardiac Life Support (ACLS) therapy for a toxic dose of four selected drugs. The purpose was to determine the optimal combination of lipid rescue and traditional ACLS therapy for treatment overdose of bupivacaine, desipramine, venlafaxine and bupropion.

Design: This study was a prospective, experimental, mixed research design

Methods: For each drug studied, seven swine were assigned to eight ACLS or BLS protocol resuscitation groups: Vasopressin/Lipid; Epinephrine/Lipid; Lipid; Epinephrine; Vasopressin; Epinephrine/Vasopressin; Epinephrine/Lipid/Vasopressin; and CPR. Each subject was administered a toxic dose of the drug until there was a non-perfusing arrhythmia. Each resuscitation protocol was implemented. Survival was defined as return of spontaneous circulation to a systolic blood pressure $\geq$ 60 mm/Hg.

Sample: The sample consisted of seven swine assigned to eight ACLS or BLS protocol resuscitation groups: Vasopressin/Lipid; Epinephrine/Lipid; Lipid; Epinephrine; Vasopressin; Epinephrine/Vasopressin; Epinephrine/Lipid/Vasopressin; and CPR.

Analysis: An odds/ratio was used to analyze the data.

Findings: As expected, the results varied according to the studied drug overdose. For example, with bupivacaine, seventy-one percent of the epinephrine/lipid group survived compared to 19% of all the groups without lipid therapy. The odds of survival for the epinephrine with lipids group was 8.5 fold greater than all the groups without lipid therapy. Epinephrine with lipid group had a five times greater odds for survival compared to epinephrine with vasopressin. Epinephrine alone offered a 4.5 times greater chance of survival when compared to the group that received lipid alone. No swine in the CPR or vasopressin group survived. With the desipramine study, 100% of the vasopressin group survived, whereas none of the epinephrine group survived ($p>.05$).

Implications for Military Nursing: There have been many thousands of soldiers wounded in the face of battle. Our military medical system is diligently trying to adequatly treat the needs of these soldiers. The major needs include physical (pain) and psychological stress (depression, PTSD, etc.). This psychological stress on our soldiers intensifies with increased deployments. As such, there has been an increased use of anti-depressants, and tricyclic drugs to treat both depression and pain. Unfortunately, suicide rates (with some overdosing on these medications) have dramatically increased in our soldiers and have become a major issue with the Army, Department of Defense and Congress. This research grant offers possible treatment options for those individuals that have received a lethal toxic dose of the four selected drugs. It is imperative to be able to resuscitate patients from these potential lethal toxicities

TSNRP Research Priorities that Study or Project Addresses

Primary Priority

Force Health Protection:	☐ Fit and ready force ☐ Deploy with and care for the warrior ☐ Care for all entrusted to our care
Nursing Competencies and Practice:	☒ Patient outcomes ☐ Quality and safety ☐ Translate research into practice/evidence-based practice ☐ Clinical excellence ☐ Knowledge management ☐ Education and training
Leadership, Ethics, and Mentoring:	☐ Health policy ☐ Recruitment and retention ☐ Preparing tomorrow's leaders ☐ Care of the caregiver
Other:	☐

Secondary Priority

Force Health Protection:	☐ Fit and ready force ☐ Deploy with and care for the warrior ☐ Care for all entrusted to our care
Nursing Competencies and Practice:	☐ Patient outcomes ☐ Quality and safety ☒ Translate research into practice/evidence-based practice ☐ Clinical excellence ☐ Knowledge management ☐ Education and training
Leadership, Ethics, and Mentoring:	☐ Health policy ☐ Recruitment and retention ☐ Preparing tomorrow's leaders ☐ Care of the caregiver
Other:	☐

Progress Towards Achievement of Specific Aims of the Study or Project

Findings related to each specific aim, research or study questions, and/or hypothesis:

Theoretical Framework
The theoretical framework for this study is the integration of lipid rescue with traditional treatment modalities for toxic levels of lipophilic drugs. The lipophilic drugs that this study will investigate are a local anesthetic (bupivacaine) and antidepressants (bupropion, desipramine, and venlafaxine). Overdose of these drugs can lead to cardiovascular collapse that is difficult or impossible to resuscitate with traditional ACLS protocols. Lipid rescue therapy is promising, but results from previous studies are mixed particularly when given in combination with epinephrine. The addition of epinephrine appears to negate the benefits of lipid rescue therapy. Previous studies have utilized high dose epinephrine or sustained hypoxia or lipid soluble anesthesia drugs, which resulted in inconclusive results. This study will determine the optimal combination of traditional ACLS drugs and lipid rescue. This combination will yield the highest probability of returning to spontaneous circulation after overdose of these lipophilic drugs (FIGURE 1)

Subject and Scope of Study
Toxic doses of highly lipophilic drugs specifically local anesthetics (bupivacaine) and antidepressants (bupropion, desipramine, and venlafaxine) are often deadly. Using the US poison control data of 82,802 suicidal single agent ingestions from 2000-2004, there were 40 major or fatal outcomes per 1000 reported antidepressant ingestions (White, 2008). The most devastating complication of these drugs is a non-perfusing cardiac arrhythmia and ultimately asystole. When cardiac toxicity occurs, resuscitation is difficult, prolonged, and usually fatal. With widespread use of these drugs in the military in the treatment of PTSD (Posttraumatic stress disorder), depression and TBI (Traumatic brain injury), it is of paramount importance to find methods for effective resuscitation. Until recently, cardiopulmonary bypass was the only method in effectively treating cardiac arrest from these drugs (Weinberg, 2008). Infusion of lipid emulsion may be effective in treating an otherwise fatal complication per anecdotal documentation. The proposed mechanism of action of lipid therapy is not known but is thought to be a combination of reduced tissue binding by re-established equilibrium in the plasma lipid phase and a beneficial energetic-metabolic effect. Weinberg (2008) stresses that future areas of investigation should focus on improved treatment regimens and better understanding of the mechanism of lipid therapy.

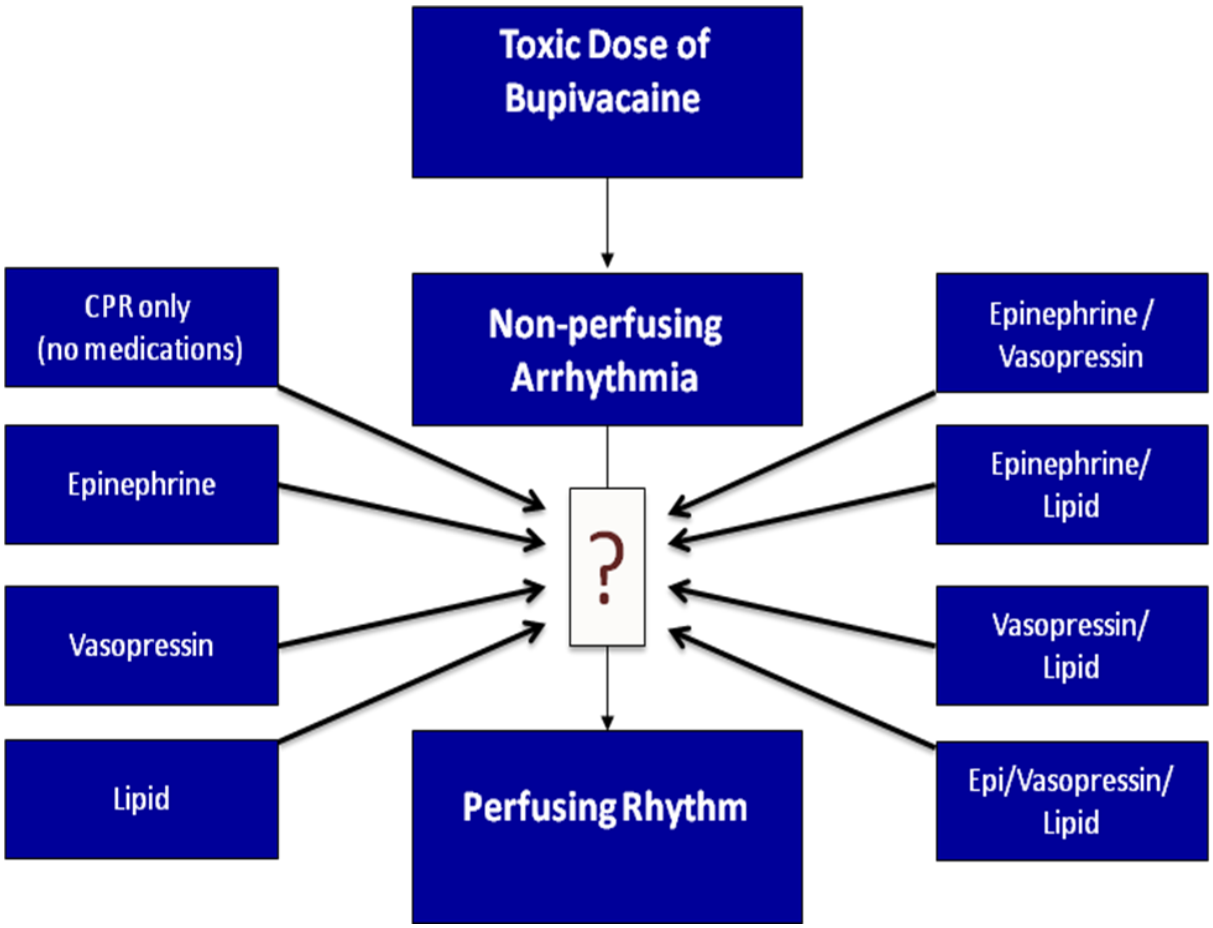
This multi-year study had been divided into 4 parts, with a drug completed each year. Each part will consist of examining one drug (toxic IV dose) and the best resuscitation model for survival. We have compared eight different resuscitation methods after each swine received a toxic dose of Bupivacaine, Desipramine, Bupropion and Venlafaxine.

Specific Aims of the Grant
1. Determine if the addition of lipid rescue therapy is effective for the treatment of bupivacaine, Desipramine, Bupropion and Venlafaxine overdose as tested by a combination of lipid therapy and traditional ACLS interventions.
2. What are the odds ratios of survival between the groups?
3. Determine what the effects of lipid rescue therapy are on the pharmacokinetics of the local anesthetic bupivacaine to find if there is supporting evidence for the "lipid sink" theory of how lipid rescue therapy facilitates resuscitation of bupivacaine overdose.

Research Questions
To meet these aims, the following research questions were generated and will guide the study:

1. Is there a statistically significant difference in survival between the eight interventions (with and without lipid emulsion) given a toxic dose of these drugs.
2. Is there a statistically significant difference in the pharmacokinetics of toxic doses of bupivacaine given lipid emulsion therapy?
3. What are the odds ratios of survival between the groups?

BUPIVACAINE:

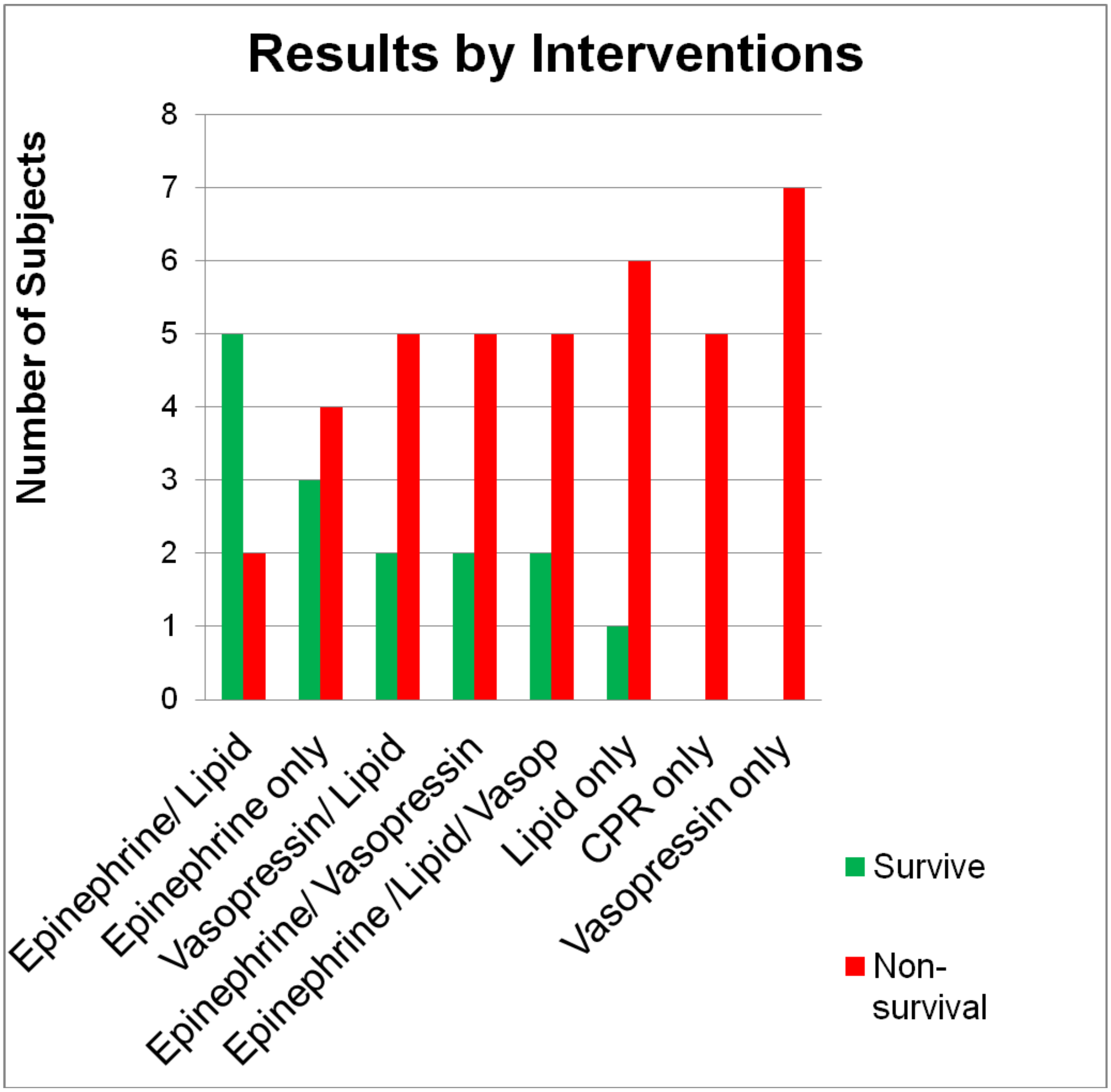


(FIGURE 1 THEORETICAL FRAMEWORK)

Multivariate analyses of variance were used to determine if the groups were equally distributed concerning pre-intervention (weight, temperature, vital signs) data. The post-intervention data was analyzed using an odds ratio (chance of survival) to determine odds of survivability between the groups. Additionally, a Chi-Square test was used to test for statistical significance differences among groups. Means and standard deviations from a previous study were used to calculate an effect size. The investigators also used G-Power 3.0.10 to determine the sample sizes needed in the bupivacaine experiment. Using an alpha of 0.05, power of .80, and a large effect size, 0.6, the number needed was determined to be seven per group.

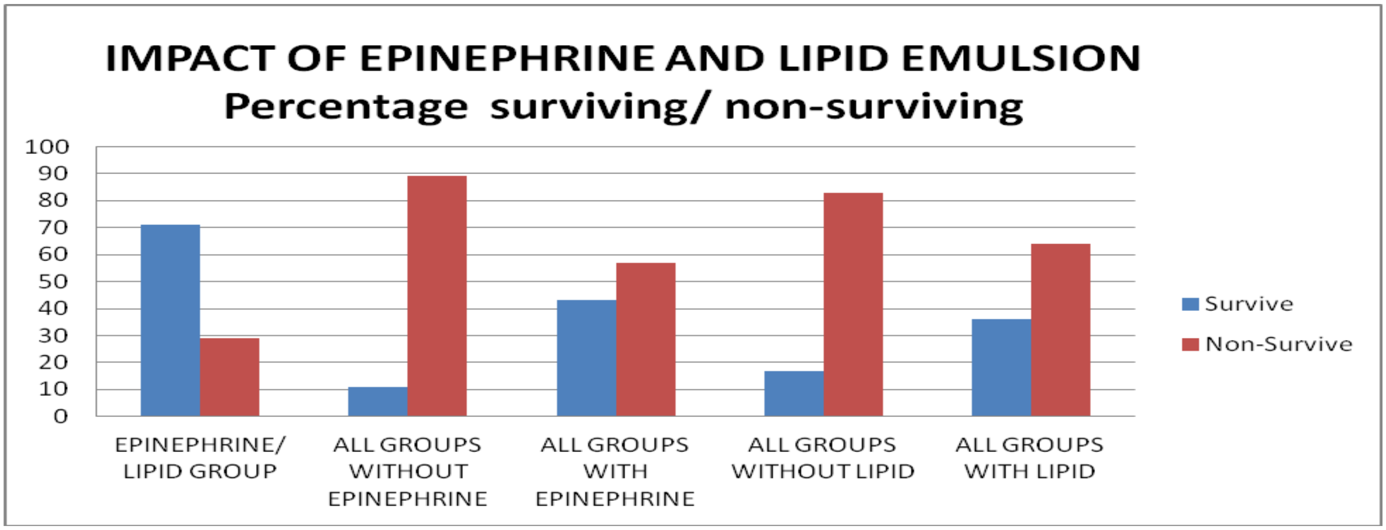
Results: A total of 54 animals were included in the research. A MANOVA was used to analyze the pretest variables of all laboratory values, weight, vital signs and NPO deficit replacement. There were no statistically differences between the groups ($p > .05$) indicating all groups were equivalent relative to these stated parameters. The CPR only group was purposely reduced to five swine (instead of 7) because of the lethality of the model and zero probability that any swine in that group would recover in order to reduce the number of swine used.

The epinephrine and lipid emulsion group had the greatest number of survivors with five of the seven swine surviving. The Epinephrine only group yielded three survivors and the Lipid emulsion only group yielded one survivor. No swine in the CPR only or Vasopressin only groups survived. Graph 1 outlines the results of survivability between intervention groups.



GRAPH 1, EXPERIMENTAL RESULTS

The impact of Epinephrine and Lipid emulsion, both alone and in combination, with regard to treatment of bupivacaine toxicity is depicted in Graph 2. Seventy one percent of the animals in the Epinephrine/Lipid emulsion group survived compared to 19% of all the groups without Lipid emulsion therapy (p = 0.008). The chances of survival for the Epinephrine/Lipid emulsion group was 3.7 fold greater than all the groups without Lipid emulsion therapy. Furthermore, there was a statistically significant difference relevant to survival between the Epinephrine/Lipid emulsion group and the CPR only group (p=0.028); and when compared with the Vasopressin group (p=0.05).



GRAPH 2, IMPACT OF EPI AND LIPID

Comparison of the chances of survival of different ACLS regimes given a toxic dose of bupivacaine is listed in Table 1. In comparing the group that represents group 1 to the group the represents group 2, group 1 has a greater likelihood of survival, which is represented by the chances of survival number. For example, there is a 15 times greater odds of survival of bupivacaine toxicity if one used epinephrine and lipid emulsion vs. using lipid emulsion alone. Chi-square results of comparisons of selected groups are listed in the last column of Table 1.

ODDS RATIO OF SURVIVIAL, SELECTED COMPARISIONS OF GROUPS

Group 1	**Group 2**	**Chances of survival**	**Chi-square**
Epinephrine (all groups with epinephrine)	No epinephrine (all groups with no epinephrine)	6.25X times greater survival (p=0.01)	p=0 .007
Lipid emulsion (all groups with lipid)	No lipid emulsion groups	2.5X (p=0.14)	p=0.13

Epinephrine alone	Lipid emulsion alone	4.5X (p=0.25)	p= 0.237
Epinephrine and lipid group	Epinephrine and Vasopressin group (Standard ACLS protocol)	6.25X (p=0.12)	p= 0.10
Epinephrine and lipid emulsion	Epinephrine, Lipid emulsion, and Vasopressin	6.25X (p=0.12)	p=0.109
Epinephrine and lipid emulsion	Epinephrine alone	3.3X (p=0.29)	p=0.28
Epinephrine and lipid emulsion	Lipid emulsion alone	15X (p=0.05)	p=0.03
Epinephrine and lipid emulsion	No lipid emulsion groups	11.5X (p=0.01)	p=0.005

(All data was confirmed via website: http://www.medcalc.org/calc/odds_ratio.php Chi-square data via SPSS software.)

TABLE 1, ODDS OF SURVIVAL

One other notable result of the study was the time of return to spontaneous circulation for the swine that did survive. As shown in Table 2 it also appears that not only did the Epinephrine/ Lipid group have the greatest number of swine that returned to spontaneous circulation, but also they returned faster. The mean time for return of spontaneous circulation for that group was 4 minutes. Although this rapid response is two-seven times faster than the other survivors in the other groups, the small number of survivors overall (small n) may be an issue. However, the trend is apparent that this drug combination not only offers increased survivability, but may also deliver quicker onset to return of spontaneous circulation.

COMPARISION OF SURVIVORS MEAN TIME TO RETURN OF SPONTANEOUS CIRCULATION

GROUP	NUMBER OF SURVIVORS	MEAN TIME TO RETURN OF SPONTANEOUS CIRCULATION
Vasopressin/ Lipid	2	28 minutes after injection of bupivacaine
Epinephrine/ Lipid	5	**4 minutes** after injection of bupivacaine
Lipid only	1	14 minutes
Epinephrine/ Vasopressin/Lipid	2	13 minutes
Epinephrine/ Vasopressin	2	24 minutes
Epinephrine only	3	9.3 minutes
Vasopressin only	0	n/a
CPR only	0	n/a

TABLE 2 MEAN TIMES TO ROSC

DESPIRAMINE:

Theoretical Framework will be similar throughout study as above.

RESULTS:

A total of 56 animals were included in the research. A multivariate analysis of variance (MANOVA) was used to analyze the pretest variables of all laboratory values, weight, vital signs and nothing by mouth (NPO) deficit replacement. There were no statistically differences between the groups (p>.05) indicating all groups were equivalent relative to these stated parameters.

The vasopressin group had the greatest number of survivors with all of the seven swine surviving (100%). The vasopressin with lipid emulsion had five of the seven swine survive (71%). The epinephrine, vasopressin with lipid emulsion yielded four of the seven swine surviving (57%). Two swine survived in the lipid only group (29%) and only 1 swine survived out of seven in the epinephrine and epinephrine, vasopressin groups (14%). No swine in the CPR only group or epinephrine with lipids survived (0%). Figure 1 outlines the results of survivability between the eight individual intervention groups.

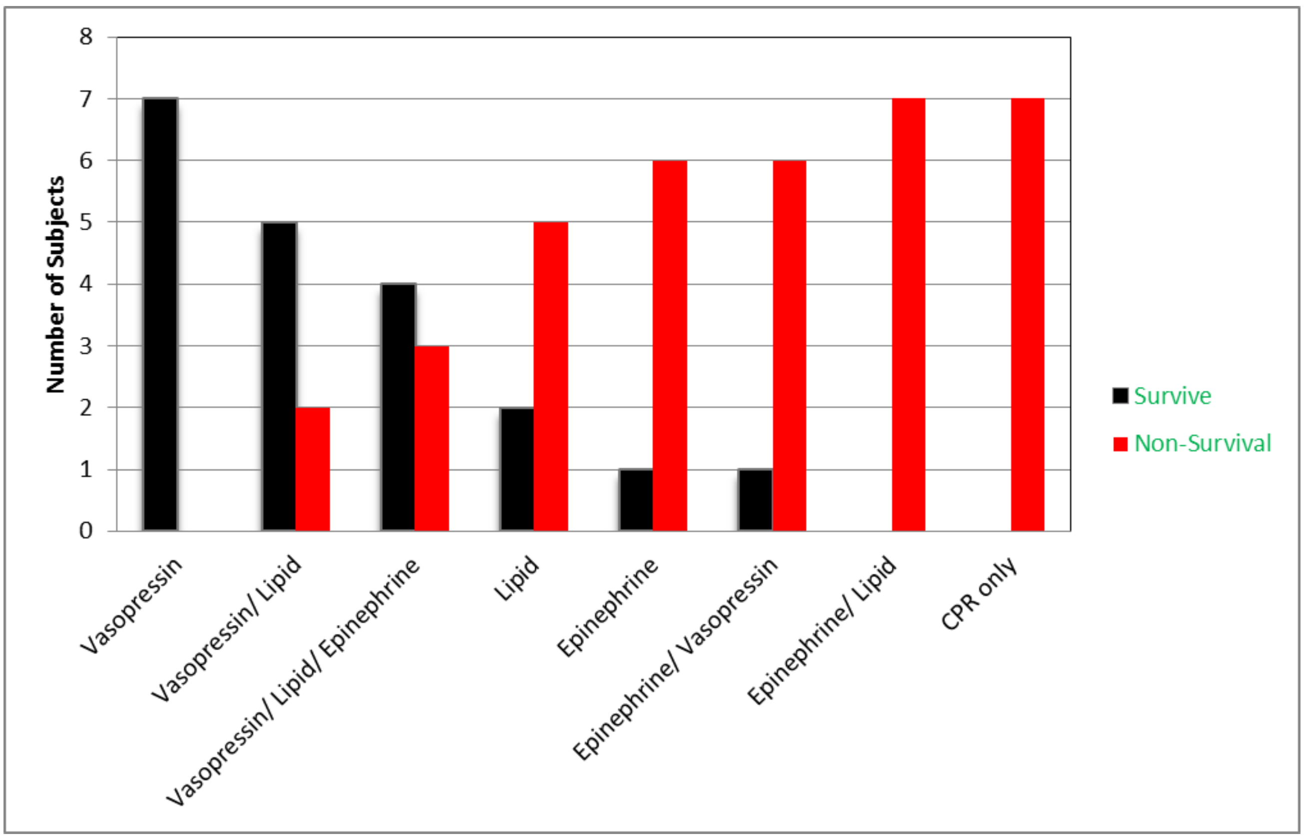


FIGURE 1, RESULTS BY INTERVENTIONS

Vasopressin and Epinephrine are the major ACLS drugs used in resuscitation. Figure 2 depicts the survival differences between these two drugs when each drug groups are combined. (Vasopressin with Vasopressin and Lipid vs. Epinephrine with Epinephrine and Lipid) Almost 86% of the animals in the

vasopressin and vasopressin/ lipid groups combined survived. In contrast, and surprisingly, only 7% of the swine in the epinephrine and epinephrine/ lipid groups survived (p=.0007). Alternatively, from a different perspective there is a 65 odds ratio of surviving with a desipramine overdose if treated with vasopressin instead of epinephrine only (p=.015). Likewise comparing the vasopressin groups with and without lipids vs. epinephrine with and without lipids there is a 78 odds ratio of survival (p=.0007) with the former combined groups. Furthermore, there was a statistically significant difference relevant to survival between the Vasopressin group and the CPR only group (p=.0087), when compared to the Lipid only group (p=.03) and when compared to the Epinephrine / Vasopressin group (p=.015).

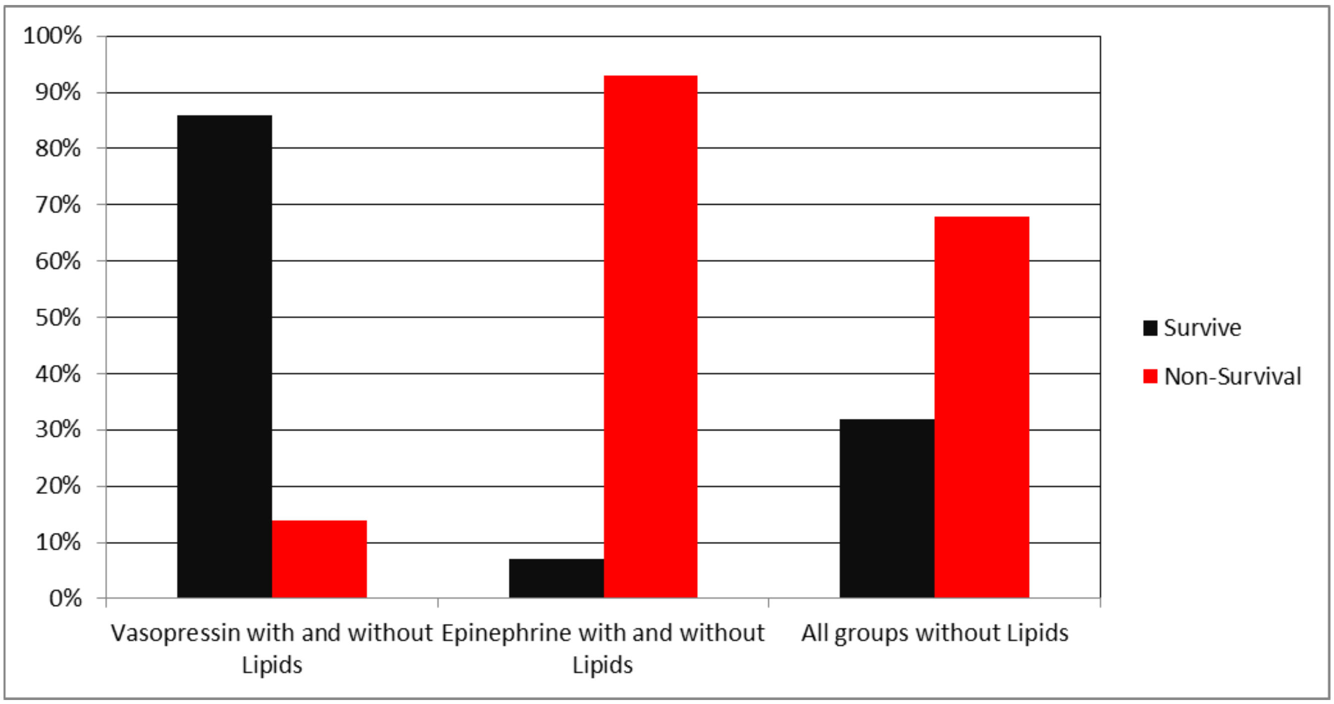


FIGURE 2, IMPACT OF VASOPRESSIN WITH AND WITHOUT LIPIDS

Comparison of the chances of survival of different ACLS regimes with this swine model given a toxic dose of desipramine is listed in Table 1. In comparing the group that represents group 1 to the group that represents group 2, group 1 has the greater likelihood of survival, which is represented by the odds ratio of survival number. For example, there is a 65 times greater odds of survival of desipramine overdose if one used vasopressin vs. epinephrine only. Chi-square or Fisher's Exact test results of comparisons of selected groups are listed in the last column of Table 1.

Group 1	Group 2	Odds ratio of survival	Chi-square or Fisher's Exact test
Vasopressin (all groups with vasopressin)	No Vasopressin (all groups with no vasopressin)	12.9 X times greater survival	(p=0.000)
Lipid emulsion (all groups with lipid)	No Lipid emulsion groups	1.37X	(p=0.252)
Vasopressin only	Epinephrine only	65X	(p=0.001)
Vasopressin/ Lipid group	Lipid only	6.25X	(p=0.109)
Vasopressin only	Vasopressin/ Lipid	6.8X	(p=0.127)
Vasopressin/ Lipid/ Epinephrine	Epinephrine	8X	(p=0.266)
Vasopressin/ Lipid	Epinephrine/ Lipid	33X	(p=0.02)

TABLE 1, ODDS RATIO OF SURVIVAL AND CHI-SQUARE RESULTS

VENLAFAXINE:

Theoretical Framework will be similar throughout study as above.

RESULTS:

In this study, 56 piglets were investigated. Pre-test laboratory values, as well as total amount of venlafaxine per kilogram of body weight administered and resulting arterial blood gasses were monitored during the procedure.

Survival was noted in seven of the eight groups. The greatest survivability resulted from the combination of vasopressin with lipid emulsion, with five subjects obtaining ROSC. Utilization of vasopressin alone yielded four-subject survivability, closely followed by the epinephrine alone group resulting in three-subject survivability. There was no difference in the remaining groups with the exception of the epinephrine, vasopressin, and lipid combination, where all seven subjects expired. (Chart 1)

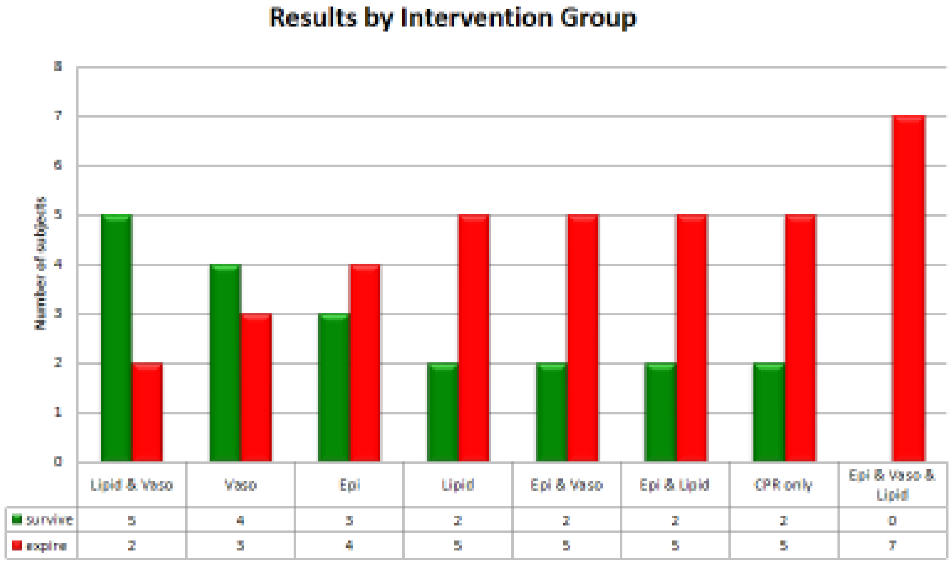


CHART 1, RESULTS BY INTERVENTION GROUP

Percent survivability was calculated based on various integrations of the experimental combinations. Greatest survivability (70.1%) was noted with the vasopressin and lipid emulsion group. Any subsequent group that utilized vasopressin therapy, or did not use lipid emulsion, was noted to have 39.3% survivability. There was no large variation in the remaining combinations of the interventions, with the exception of the sole use of epinephrine resulting in 25% survivability. (Chart 2)

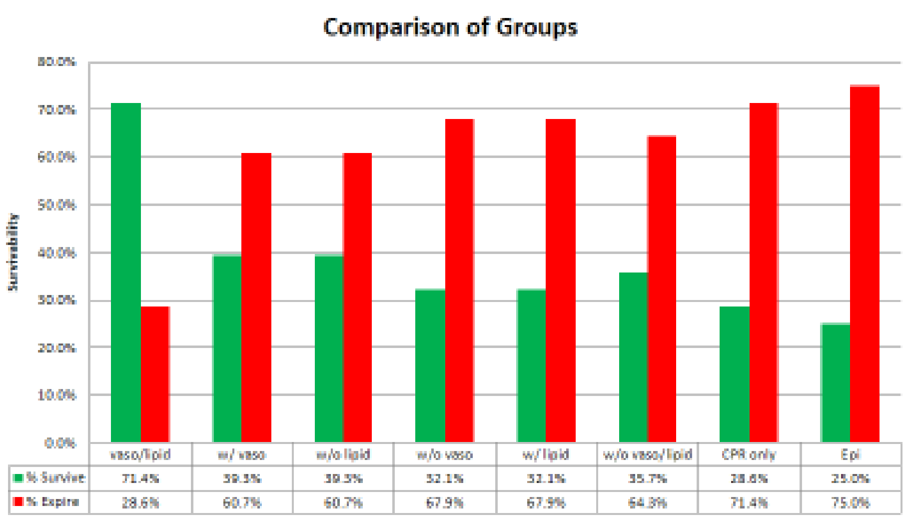


CHART 2, COMPARSION OF SELECTED GROUPS

Odds Ratio was performed, and it was observed that there was a 33 times greater survivability with the vasopressin and lipid emulsion group when compared to the epinephrine, vasopressin, and lipid emulsion combination (95% CI, P=0.0338). Vasopressin and lipid emulsion when compared to lipid emulsion alone resulted in an odds ratio of 6.25 (95% CI, P=0.1214). When compared to epinephrine alone, vasopressin and lipid emulsion continued with an odds ratio of 3.33 (95%CI, P=0.2879). Complete results of odds ratio can be seen in (Table 2).

	VASO/LIPID: EPI	VASO/LIPID: VASO	VASO/LIPD: LIPID	VASO:EPI	VASO/LIPID: VASO/LIP/EPI	LIP: NO LIPID	VASO: NO VASO
SURVIVE/ EXPIRE	5/2: 3/4	5/2: 4/3	5/2: 2/5	4/3: 3/4	5/2: 0/7	9/19: 11/17	11/17: 9/19
ODDS RATIO	3.3333	1.875	6.25	1.778	33	0.7321	1.366
95% CI	0.3619 to 30.7025	0.2036 to 17.2702	0.6148 to 63.5410	0.2140 to 14.7672	1.3059 to 833.9222	0.2443 to 2.1935	0.4559 to 4.0930
Z STATISTIC	1.063	0.55	1.549	0.533	2.122	0.557	0.557
P	0.2879	0.579	0.1214	0.5943	0.0338	0.5775	0.5775

TABLE 2, ODDS RATIO OF SURVIVAL

BUPROPION:

Theoretical Framework will be similar throughout study as above.

RESULTS

Statistical analyses of the data were performed in IBM SPSS version 21 and Microsoft Excel. Both descriptive and inferential statistical analyses follow.

Descriptive statistics for the subjects at baseline are show in Table 1. The subjects weighed between 55kg and 76kg, with a mean of 66.63 kg. The average heart rate was 84.79 bpm with a large range of 70 bpm. Table 3 provides the means by group at baseline. This table illustrates the high degree of similarity among the groups. Randomization worked to control for baseline characteristics of the swine.

TABLE 1, DESCRIPTIVE ANALYSIS OF SUBJECTS

No. Obs = 56	Min	Mean	Median	Max	s	Skewness
kg (weight)	55.00	66.63	66.50	76.00	5.95	-0.25
End-Tidal CO2	33.00	40.52	40.00	46.00	2.59	0.16
Ventricular Return	450.00	602.32	600.00	750.00	71.36	0.22
RR Interval	9.00	11.16	11.00	14.00	1.04	-0.33
O2 Saturation	94.00	98.93	99.00	100.00	1.20	-1.93
Heart Rate	58.00	84.79	83.00	128.00	13.56	0.65

Systolic	75.00	107.14	106.00	171.00	16.54	0.92
Diastolic	48.00	73.43	73.50	110.00	13.39	0.41
Mean Arterial Pressure	48.00	86.64	88.00	122.00	15.53	0.03
Cardiac Output	2.40	9.65	7.00	71.00	12.49	4.02
Temperature	34.90	36.65	36.70	38.20	0.64	-0.30

TABLE 2
MEANS BY GROUP

No. Obs = 56	CPR	VASO/LIPID	EPI ONLY	VASO ONLY	LIPID ONLY	EPI/VASO ONLY	EPI/VASO/LIPID	EPI / LIPID
kg (weight)	66.29	66.86	70.00	66.00	65.71	65.14	66.29	66.71
End-Tidal CO2	39.86	41.71	39.86	40.43	41.43	39.29	40.86	40.71
Ventricular Return	599.29	622.14	640.00	582.14	626.43	579.29	590.00	579.29
RR Interval	10.86	10.86	11.14	11.71	11.00	11.14	11.29	11.29
O2 Saturation	99.43	99.29	98.00	98.71	98.71	98.71	99.00	99.57
Heart Rate	83.29	84.29	77.86	93.14	82.00	85.71	92.00	80.00
Systolic	103.43	105.14	96.86	119.29	106.14	103.43	118.29	104.57
Diastolic	75.43	74.43	63.14	79.43	72.57	67.29	84.71	70.43
Mean Arterial Pressure	80.71	87.71	76.00	95.29	88.00	81.29	98.71	85.43
Cardiac Output	12.40	14.16	5.76	7.77	6.79	6.79	7.49	16.03
Temperature	36.80	36.66	36.34	36.34	36.89	36.66	36.90	36.61

Table 3 provides mean survival (a proportion) and mean ROSC time given that the animal survived by group. A few findings from this descriptive analysis follow. The entire control group failed to recover as expected. There were also no survivors from the "lipid only" group. Since 0.46 of the total population survived, the probability of achieving zero successes in seven trials might be modeled as a hypergeometric random variable (X) with parameters n = sample size, S=sample successes, and N = population size (also known as Fisher's Exact test). The probability of obtaining a result this extreme is then P(X=0 | n=7, S=26, N=56, X~Hyp) = .009 which is less than □=.05. We reje deaths in seven trials is due to chance alone. Lipids alone did not allow for recovery. Further, we notice that all combinations involving epinephrine resulted in survival above the expected proportion. In fact, the number of survivors involving groups that had epinephrine was 22 versus six deaths. The probability of obtaining a result this extreme or more extreme when modeled as a hypergeometric is P (X≥22 | n =28,

S=26, N=56, X~Hyp) ≤ .00001. Epinephrine combinations appear to be effective. Vasopressin when not combined with epinephrine resulted in a survival proportion of 29% (4 out of 14 pigs). P(X≤4 | n =14, S=26, N=56) ≤ .107, so there is insufficient evidence to assume performance of the drug different from the mean.

The table also illustrates that the fastest mean ROSC given an animal survived was 7 minutes (epinephrine combined with lipids), while the next best option appeared to be epinephrine only with a mean time of 10.33 minutes. Additional analysis using a Cox proportional hazards model investigated this potential difference (discussion to follow).

Table 3. Dependent variables, survival proportion and ROSC for animals that survived

Group	Survival proportion	ROSC
CPR	0.00	N/A
VASO/LIPID	0.29	19.00
EPI ONLY	0.86	10.33
VASO ONLY	0.29	19.00
LIPID ONLY	0.00	N/A
EPI/VASO ONLY	0.86	17.00
EPI/VASO/LIPID	0.86	13.00
EPI/LIPID	0.57	7.00
Total	0.46	13.31

Table 4 illustrates a contingency table for epinephrine combinations versus all other options. The odds for survival given the use of epinephrine in comparison to other options were (22/6)/(4/24) = 22:1. The 95% confidence interval for this odds ratio is (5.47, 88.43). Epinephrine appears to improve survival.

Table 4. Contingency table for survival based on epinephrine use

	Lived	Died	Total
No Epinephrine	4	24	28
Epinephrine	22	6	28
Totals	26	30	56

We then generated a logistic regression model by amalgamating those groups with less than a .46 (mean) survival proportion and comparing against the remaining groups. The base group included CPR, lipid only, vasopressin only, vasopressin/lipid.

The initial classification table under the null assumes that all swine die, because the mean survival is .46. Making this assumption results in 54% classification accuracy, 100% accuracy for the 30 who died and 0% accuracy for the 26 survivors. Running the logistic regression, we found a statistically significant model (= 27.59, $p<.001$) that captured 52% of the pseudo-variance (Nagelkerke R2=.520). The classification table after the model’s implementation correctly classified 82.1% of all observations, 80% of non-survivors and 84.6% of survivors. This improvement is non-trivial. The bootstrapped coefficients resulting from 1990 converging samples out of 2000 are in Table 5.

Table 5. Coefficient table for the logistic regression of group on survival

	B	S.E.	Wald	df	p	Exp(B)	95% CI for EXP(B)	
Groups			19.263	4	0.001			
Epi only	3.584	1.208	8.806	1	0.003	36.000	3.376	383.907
Epi / Vaso	3.584	1.208	8.806	1	0.003	36.000	3.376	383.907
Epi / Vaso / Lipid	3.584	1.208	8.806	1	0.003	36.000	3.376	383.907
Epi / Lipid	2.079	0.935	4.942	1	0.026	8.000	1.279	50.040
Constant	0.774	0.418	3.425	1	0.064	2.169		

To investigate the potential time to recovery differential that we noticed in the epinephrine/lipid and epinephrine groups, we combined substandard survival groups, those with less than the average survival proportion of .46, into a single set (CPR, lipid only, vasopressin/lipid, and vasopressin only). We also combined those treatments near or below the mean treatment time (vasopressin, epinephrine/vasopressin/lipids). The epinephrine only and epinephrine/lipid group remained ungrouped for comparison of their efficacy in a Cox proportional hazards model.

Results of the global test for the regression were statistically significant, -2LL = 120.85, = 8.14, p=.043. We then bootstrapped coefficient estimates (due to the sample size) for the Cox regression model using the below average survival group as the comparative base. The number of converging iterations from 2000 selected was 1939.

The coefficient table is Table 6. Only the epinephrine/lipid variable belongs in the model, as it has a p-value of .015. The cumulative graph of ROSC by group and by time is Figure 2.

Table 6. Coefficient table for the Cox proportional hazards model

	B	exp(B)	SE	p
Vasopressin, Vasopressin/Lipid	0.508	1.662	1.789	0.303
Epinephrine only	1.148	3.151	1.932	0.068
Epinephrine / Lipids	1.893	6.637	2.922	0.007

Figure 1a. Percentage of subjects that achieved ROSC per treatment group

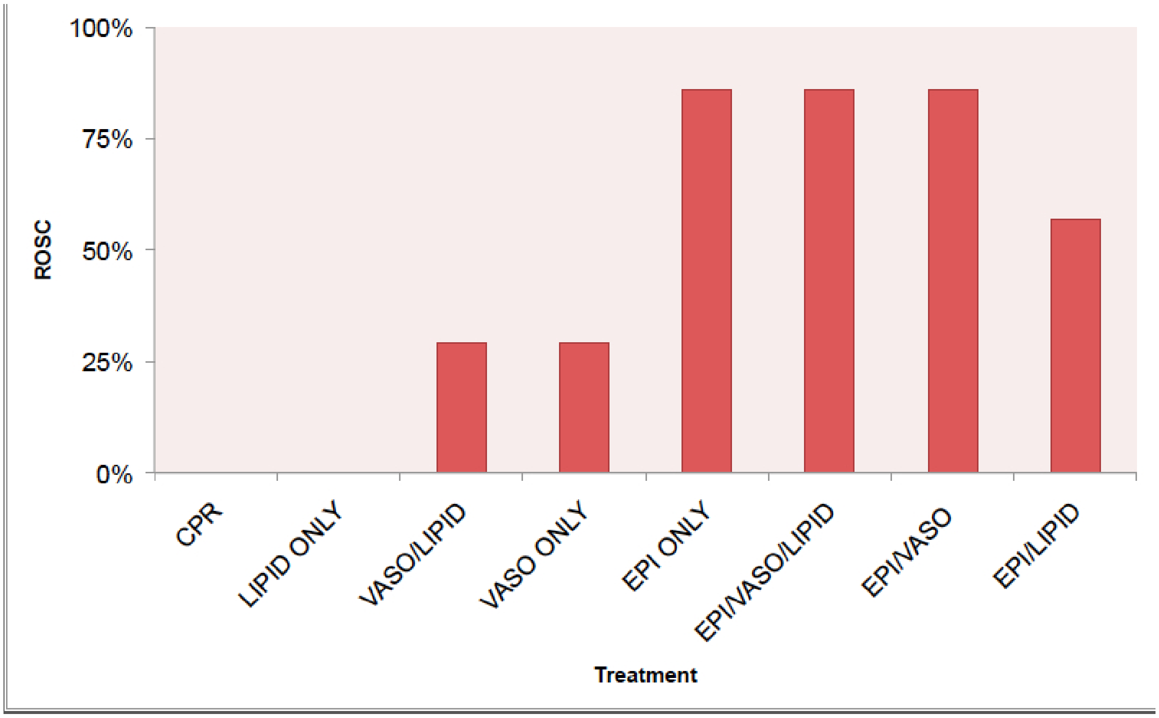


Figure 1b. Minutes to ROSC per treatment group

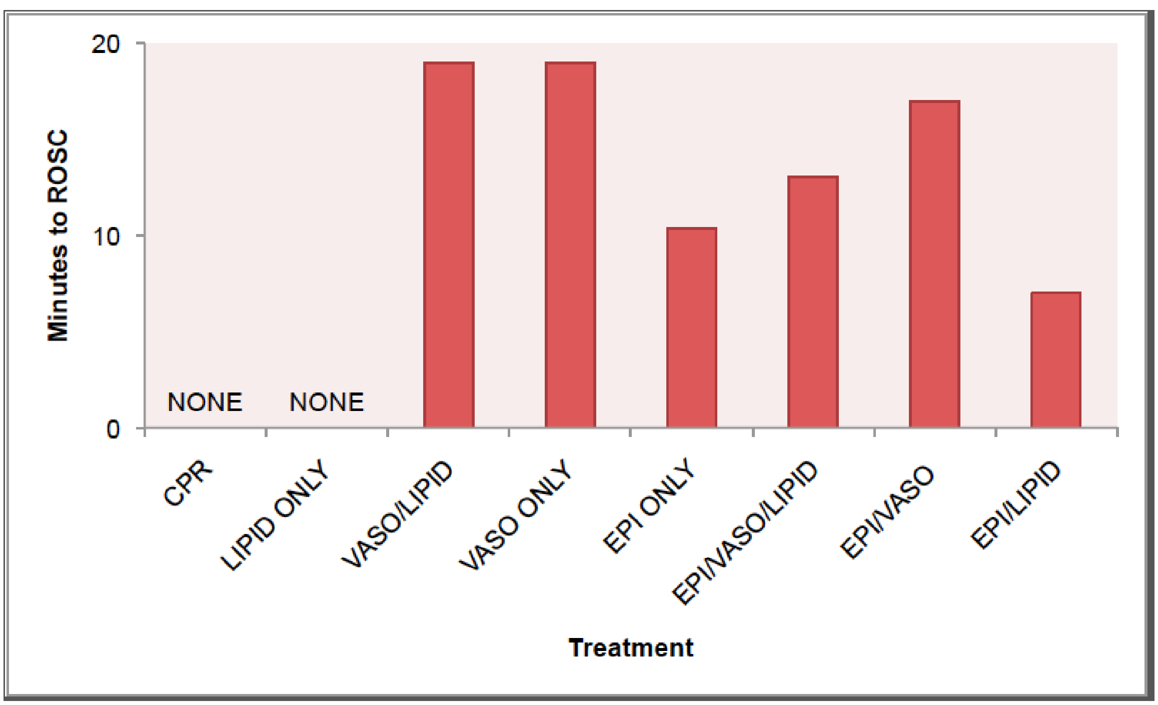
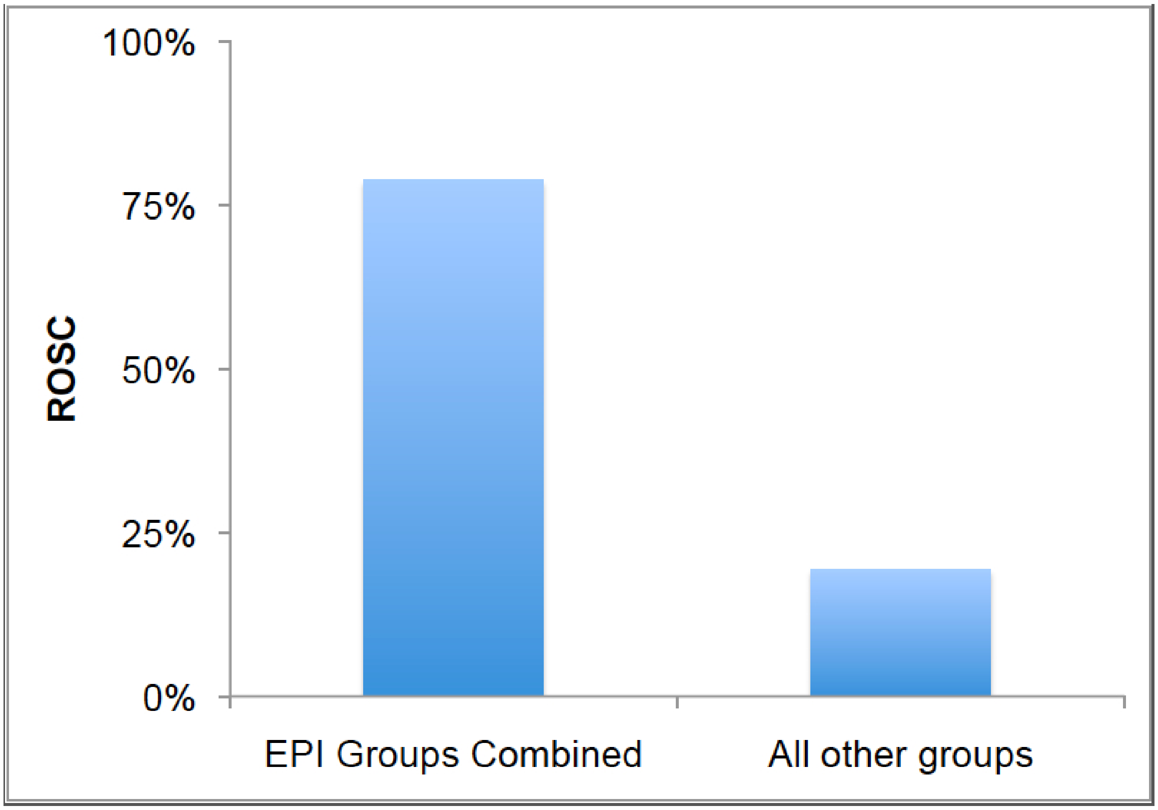


Figure 1c. ROSC in subjects that received epinephrine vs. no epinephrine



We evaluated ROSC in eight different treatment protocols incorporating ACLS with or without lipid rescue in bupropion toxicity. Our findings suggest that the odds of survival when epinephrine was administered alone or in any combination was 22x higher compared to when no epinephrine was administered (95% confidence interval). Further survival analysis suggests that time to ROSC was shortest when epinephrine was combined with lipids

Relationship of current findings to previous findings:

There are several clinical case reports that suggest evidence of the efficacy of intravenous lipid emulsion therapy in the treatment of antidepressant overdose. Finn and colleagues discuss the initial management and resultant survival of a patient following a Seroquel and Zoloft overdose. After 15 minutes of lipid infusion, the patient experienced a rapid increase in level of consciousness. Sirianni and colleagues discuss a case report where a 17 year old overdosed on bupropion and Lamictal. There was resultant cardiovascular collapse. Seventy minutes of standard ACLS was unsuccessful at restoring sustained circulation. After an intravenous bolus of lipid emulsion, an effective sustained pulse was observed as the patient survived. Furthermore, Hojer & Hulting discussed two case reports following an Effexor overdose. In both cases, both patients developed a non-perfusing cardiac arrhythmia that was refractory to ACLS protocols. No lipid infusions were initiated, and both reports ended in patient expiration.

Other articles were reviewed and it can be noted that analgesics, antipsychotics, and antidepressants are the most commonly involved substances in overdose related injury and death, according to Jamaty, Bailey, & LaRoque. They also discuss and assess the efficacy and safety of intravenous lipid emulsion in the management of poisoned patients. White, Litovitz, & Clancy discuss the increased risk for suicide

attempts, particularly by overdose, in depressed patients. Finally, Reeves, Parker, & Konkle-Parker discuss the relevance of the above-mentioned case reports as it relates to our military. PTSD and Traumatic Brain Injury (TBI), being two of the worst offenders plaguing our soldiers returning from war, are commonly treated with not only counseling, but also with a vast array of antidepressants, antipsychotics, and anticonvulsant medications.

It appears that utilizing a lipid emulsion infusion in conjunction with standard ACLS protocols (dependent on drug) has an increase in the odds ratio of survival. It is not the magical bullet that was anticipated it would be, but it appears that lipid emulsion therapy does have a place in an emergency setting for toxic levels of lipophilic drugs.

Effect of problems or obstacles on the results:
Swine are physically and anatomically very similar to humans and their ease of use has made them used widely in resuscitation protocols. With that stated, it should be noted that recently there has been some issues related to using swine in lipid resuscitation models. In our study, as well as the study by Niiya, some of our swine exhibited a transient red mottling rash after administration of the lipid infusion. Therefore, before initiating this study, we performed a small study examining IgE, IgG, C - reactive protein, blood gas analysis and cardiovascular parameters to determine if there are any changes in these parameters before and after lipid infusions. We found that there were no significant changes in any of our measured parameters before and after lipid emulsion infusions. Although these tests were not 'CARPA' (complement activation-related pseudo allergy) specific, there was no CARPA- like reactions with major cardiovascular changes. Swine have been shown to have consistent major cardiovascular depressive changes after liposome / nanoparticle infusions. (Liposome and nanoparticle solutions have been tested as vehicles with other drugs (narcotics, antibiotics and chemotherapeutics) to increase their half-life and effectiveness.) It has been hypothesized that swine may also have CARPA like reactions (major cardiovascular depression) after lipid infusions. Other studies have shown a transient increase in pulmonary hypertension has occurred with all swine exposed to liposomes/ nanoparticles with significant decreases in systemic arterial pressures. This decrease in SBP did not occur with our infusion of lipids, therefore, offering the possibility that this swine model may be suitable for lipid infusion experiments. However, with this said, we may not of had the impact we expected with lipid emulsions utilizing the swine model. The red mottling of the skin, gives our research team pause as it may indicate that there may be some other negative effect from the lipid infusions that we are not aware.

Limitations:
This study was done exclusively on male swine. As such, generalizations about the results regarding females cannot be made. Also as described above, using a swine model for this study may not be applicable to humans. Anecdotal evidence with human case studies from overdosing of these drugs seems to support our results. Our research team assumed that we would have a much more robust effect from lipid infusions. Given another species (goat?) or model, our results with some of the interventions may have been more definitive. There was no equipment malfunctions or attrition rates and the swine were properly randomized.

Conclusion:

This grant adds to the growing body of knowledge about the efficacy of lipid emulsion treatment in acute lipophilic drug overdose. More importantly, it examined the effects of lipid emulsions combined with ACLS protocols in restoration of cardiac function following four different drug overdoses. The results of

this research are consistent with case study findings in humans that suggest lipids are potentially useful when other ACLS interventions failed. Additionally, these results are consistent with other studies suggesting that lipids alone may lack clinical effect in the setting of acute overdose. Therefore, based on these data, management of acute antidepressant toxicity should include the use of CPR with epinephrine/ vasopressin and lipid emulsion. Research should continue to examine optimal drug dosing and timing, as well as various concentrations of lipid emulsion therapy for clear benefits in resuscitation of in the fact of acute drug toxicity.

Significance of Study or Project Results to Military Nursing

The United States is at war fighting on two fronts. Life saving advances in body armor, rapid medical evacuation from point of injury, availability of blood products, improved surgical and critical care capability and the rapid air evacuation of casualties have contributed to less than 10% mortality from wounds suffered in combat in both Iraq and Afghanistan. However, the achievement of low mortality has resulted in other problems particularly in the management of acute pain and psychological stressors. To date there have been many thousands of soldiers wounded, both physically and psychologically in the face of battle. Our military medical system is diligently trying to treat the needs of these soldiers. The major needs include physical (pain) and psychological stress (Depression, PTSD, etc.). Increased use of regional anesthesia has been very effective versus use of increased narcotics for pain. However, accidental venous or arterial injection of local anesthetics can be fatal. Lipid emulsion injections have saved many lives.

The psychological stress for our soldiers intensifies with increased deployments. As such, there has been an increased use of antidepressants, and tricyclic drugs to treat both depression and pain. In an Army study group returning from Iraq, 19.5% reported perceiving they had a moderate or severe mental health problems. Unfortunately, suicide rates (with some overdosing on these medications) have dramatically increased in our soldiers and have become a major issue with the Army, Department of Defense and Congress. Adequate short-term and long term pain-relief both remain a challenge. The object of this study was to compare effective treatments in the accidental overdose of a local anesthetic used for pain control, and methods to effectively revive patients who attempt suicide by overdosing on antidepressant medications. Over a four year period in the civilian sector, 28% of suicidal ingestions involved antidepressants. The incidence of attempted suicides with the commonly prescribed antidepressant, bupropion, is over 9%. A comparative study utilizing standard resuscitation drugs and lipid emulsion infusions in the challenge of toxic doses of lipophilic medications has never been investigated.

In a study by White and associates of over 82,000 suicidal single agent ingestions of the 25 major types of antidepressants currently available in the US, there were 40 major or fatal outcomes per 1000 cases. The hazard index was higher for tricyclic antidepressants (example, desipramine) and the atypical antidepressant bupropion. The drugs chosen for this study are popular prescribed antidepressants, with high hazard index and with IV formulations. Each of the antidepressants were chosen as a representative of their respective group,atypical (bupropion), tricyclic antidepressant (desipramine), and norepinephrine/serotonin reuptake inhibitor (venlafaxine). All of these drugs are very resistant to standard resuscitation protocol. All of the chosen drugs have had fatal outcomes from toxicity.

Bupropion has been widely prescribed as an atypical antidepressant that acts as a norepinephrine and dopamine reuptake inhibitor. The most common symptoms from overdose include sinus tachycardia, hypertension, drowsiness, lethargy, agitation, nausea and vomiting, and in particular delirium and seizures. ECG changes such as conduction disturbance and fatal lethal arrthymias have occurred.

Desipramine is a tricyclic anti-depressant that primarily prevents the re-uptake of norepinephrine. It has also been commonly prescribed to treat neuropathic pain. Overdoses of tricyclic antidepressants are difficult to treat and are extremely dangerous. Progression of symptoms includes restlessness, seizures, coma, hypoxia, hypothermia, hypotension with a prolonged QT interval or widened QRS interval often leading to lethal arrhythmias.

Venlafaxine, a serotonin and NE reuptake inhibitor is viewed as one of the safer antidepressants. Unfortunately, there are numerous case studies that exist which demonstrate that toxic doses of venlafaxine are lethal.

In summary, these lipophilic medications in toxic doses are lethal, difficult to treat, and are in need of an effective solution or treatment in the face of cardiovascular collapse. There has never been a study done to determine the effectiveness of 20% lipid emulsion infusion with and without current ACLS selected drugs and protocol.

This study along with anecdotal evidence has resulted in all anesthesia carts that are used for regional anesthesia blocks have been stocked with 20% lipid emulsion bags. Lipid infusion during accidental local anesthetic injection seems to have saved many individuals from cardiac arrest. It is hoped that lipid emulsion bags would also be available in the Emergency Room or setting to assist nurses in lethal toxicities of anti-depressants. This is not currently mandatory in hospitals to stock lipid emulsion nor military policy, but case studies and research such as this have lead more and more practicioners to utilize lipids with ACLS in these critical situations.

Changes in Clinical Practice, Leadership, Management, Education, Policy, and/or Military Doctrine that Resulted from Study or Project

None to date (see above).

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Summary of Dissemination

Type of Dissemination	Citation	Date and Source of Approval for Public Release
Publications	Johnson D, O’Sullivan J, Bolido A, Brady J, Gallahan B, Gore K, King T, Leal H, Lowery B, Stevens K. (2013) The Effects Vasopressin and Epinephrine on Cardiac Arrest Following Desipramine Overdose in a Porcine Model ***Analg Resusc: Curr Res*** S1. doi:10.4172/2324-903X.S1-012 Crane C, Sagini E, Johnson A, O’Sullivan J. Utilization of a Swine (Sus scrofa) Model for Lipid Emulsion Resuscitation Studies ISRN Anesthesiology, vol. 2012, Article ID 905034, 5 pages, 2012. doi:10.5402/2012/905034. Hudson A, Bolin S, Bishop M, Schmidt R, Johnson D, O’Sullivan J., Comparing Resuscitative Measures for Bupivicaine Toxicity Utilizing Lipid Emulsions in a Swine Model (Sus scrofa), Analgesia & Resuscitation: Current Research, 2013, http://dx.doi.org/10.4172/2324-903X.S1-006	
Publications in Press	Fulton L, Fabich R, Bhatta J, Fletcher B, Leininger K, Lienesch K, Rodriquez T, Coyner J, Johnson A, O’Sullivan J., Comparison of Resuscitative Protocols for Bupropion Overdose Using Lipid Emulsion in a Swine Model. (Submitted for publication to Military Medicine 2015) Aitken J, Avery J, Kahl B, Negron A, Chavez B, Iosett N, Johnson A, O’Sullivan J., Comparative Resuscitative Methods for Venlafaxine Toxicity in a Swine Model (Submitted for publication 2015)	

Published Abstracts	Comparative Resuscitative Methods for Desipramine Toxicity Utilizing Lipid Emulsion in Swine. Melissa Waterman, BSN; Arthur D. Johnson, RN, PhD; Joseph O'Sullivan, CRNA, PhD AANA National Conference 2013	
Podium Presentations	Hudson, A., Schmidt, R., Bolin, S., Bishop, M., Loughren, M., Johnson, A., & O'Sullivan, J. Comparative Resuscitation Measures for Bupivacaine Toxicity Utilizing Lipid Emulsions in Swine (Sus Scrofa), 2nd Annual Graduate School Research Day, AMEDDC&S, San Antonio, Texas, October 2012. Waterman, M., O’Sullivan, J. Comparing Resuscitative Measures for the Treatment of Desipramine Overdose, August 12, 2013, AANA Annual Conference, Las Vegas Best Podium Presentation: O'Sullivan, J. Comparative Resuscitation Measures for Bupivacaine Toxicity Utilizing Lipid Emulsions in Swine (Sus Scrofa), 2nd Annual Graduate School Research Day, AMEDDC&S, San Antonio, Texas, October 2012	

Poster Presentations	Hudson, A., Bolin, S., Bishop, M., Schmidt, R., Johnson, D., O'Sullivan, J., Comparing Resuscitative Measures for Bupivacaine Toxicity Utilizing Lipid Emulsions in a swine model (Sus scrofa), AANA Journal 2012. (Abstract, Poster) Countouriotis, M., Boon, P., Krum, P., Means, M., Johnson, D., Joseph O'Sullivan, J., Loughren, M., Pharmacokinetic Analysis of Lipid Rescue in a Porcine Model with Lethal Bupivacaine Toxicity, AANA Journal 2012. (Abstract, Poster) Waterman M, Johnson AD, O'Sullivan J., Comparative Resuscitation Measures for Desipramine Toxicity Utilizing Lipid Emulsion in Swine. AMSUS Convention, Seattle Washington, (Poster presentation), December 2013 Best Poster Presentation: Waterman, M., O'Sullivan, J. Comparing Resuscitative Measures for the Treatment of Desipramine Overdose, May 30, 2013, CRDAMC Research Day, Fort Hood Texas. Waterman, M., O'Sullivan, J. Comparing Resuscitative Measures for the Treatment of Desipramine Overdose, August 12, 2013, AANA Annual Conference, Las Vegas.	
Media Reports	None	
Other	None	

Reportable Outcomes

Reportable Outcome	**Detailed Description**
Applied for Patent	None
Issued a Patent	None
Developed a cell line	None
Developed a tissue or serum repository	None
Developed a data register	None

Recruitment and Retention Table

Recruitment and Retention Aspect	**Number**
Animals Projected in Grant Application	224
Animals Purchased	236
Model Development Animals	12
Research Animals	224
Animals With Complete Data	224
Animals with Incomplete Data	12

Recruitment and Retention Aspect	**Number**
Animals Projected in Grant Application	224
Animals Purchased	236
Model Development Animals	12
Animals Intervention Group / Control or Sham Group	28
Intervention Group / Control or Sham Group Animals With Complete Data	196
Intervention Group / Control or Sham Group Animals With Incomplete Data	0

Recruitment and Retention Aspect	Number
Animals Projected in Grant Application	224
Animals Purchased	236
Model Development Animals	12
Animals Intervention Group 1 / Intervention Group 2 / Control or Sham Group	See above
Intervention Group 1 / Intervention Group 2 / Control or Sham Group Animals With Complete Data	
Intervention Group 1 / Intervention Group 2 / Control or Sham Group Animals With Incomplete Data	